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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,858	11/20/2001	A. Dean Sherry	UTAD-0001	1523

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EXAMINER
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JONES, DAMERON LEVEST

ART UNIT	PAPER NUMBER
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1616

DATE MAILED: 11/10/2003

Restart

2/3/04

7

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/001,858

Applicant(s)

SHERRY ET AL.

Examiner

D. L. Jones

Art Unit

1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 March 2002 and 12 August 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 15 and 19-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14, 16-18 and 23-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 November 2001 is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.                      6) ☐ Other:

### APPLICANT'S INVENTION

1. Applicant's invention is directed to paramagnetic metal ion based macrocyclic contrast agents and uses thereof.

**Note:** Claims 1-36 are pending.

### RESPONSE TO APPLICANT'S ELECTION

2. Applicant's election without traverse of the species on page 29, Complex 2, in Paper No. 6, filed 8/12/03, is acknowledged. The restriction requirement is still deemed proper and is therefore made FINAL.

Initially, Applicant's elected species was searched. However, since no prior art was found which could be used to reject the elected species, the search was expanded to the species wherein R, R', R'', and R''' are CR<sub>1</sub>H-CO-NH-CH<sub>2</sub>-R<sub>2</sub>; R<sub>1</sub> is H; and R<sub>2</sub> is CH<sub>2</sub>COOEt (hereafter represented as EXP#1). The search *was not further* expanded because prior art was found which could be used to reject Applicant's claims.

### WITHDRAWN CLAIMS

3. Claims 15 and 19-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention/species.

### 112 REJECTIONS

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1616

5. Claims 1-14, 16-18, and 23-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, claims 1-14, 16-18, and 23-36 are ambiguous because the claims contain improper Markush terminology. For example, claim 1, line 7: "R1 includes organic substituents" is improper since proper Markush practice requires a closed list. Thus, usually the phrase 'selected from the group consisting of' or 'consisting of' is used (see MPEP 803.02 for additional information and acceptable Markush language). It should be noted that 'including' and 'comprise' are open terms and may include unnamed ingredients. Hence, Applicant is respectfully requested to make the appropriate corrections in order that one may readily ascertain what is being claimed.

Claim 16: The claim as written is confusing because it appears as if it should depend on claim 15? Please make the appropriate correction, if necessary.

## 102 REJECTIONS

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 5, 8, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Aime et al (Chem. Commun., 1999, 1047-1048).

**Aime et al** disclose the dependence of relaxivity and luminescence of gadolinium and europium amino acid complexes on hydrogencarbonate and pH (see entire document). In particular, Aime et al disclose Compound L3a (page 1047) that is encompassed in the instant invention when R, R', R'', and R''' are CR<sup>1</sup>H-CO-NH-CH<sub>2</sub>-R<sub>2</sub>; R<sup>1</sup> is H; and R<sub>2</sub> is CH<sub>2</sub>COOEt. In addition, Aime et al disclose (1) the behavior of well defined lanthanide complexes is being explored in which the metal based luminescence (Eu, Tb, and Yb) or relaxivity (Gd) is a function of a defined biochemical parameter or set of variables (pH, p(O<sub>2</sub>), or anion concentration) [page 1047, column 1]. Variable temperature 17O NMR experiments with Gd complex of L1b, L2b, and L3b allowed the mean lifetime for water exchange to be estimated. Hence, at 298 K and pH 7,  $\tau_M$ , the mean water exchange rate is greater than 1.) [pages 1047-1048, bridging paragraph]. On page 1048, columns 1-2, bridging paragraph, it is conclude that the solution behavior of the complexes is consistent with reversible chelation of HCO<sub>3</sub><sup>-</sup> at the lanthanide center wherein the bound water molecules are displaced. In the chelated ternary complex, the lanthanide ion conforms to a twisted square antiprismatic structure with a reduced helicity about the metal center (see Scheme 1, page 1048).

Thus, both Aime et al and Applicant disclose a contrast agent comprising a tetraazacyclododecane ligand structure encompassed by Applicant's claim 1.

### 103 REJECTIONS

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1616

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 1-4, 6, 7, 10-14, 16-18, and 23-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aime et al (Chem. Commun., 1999, 1047-1048) in view of Ward et al (Journal of Magnetic Resonance, March 2000, Vol. 143, pp. 79-87) and Dunand et al (J. Am. Chem. Soc., February 2000, Vol. 122, pp. 1506-1512)

**Aime et al** (see discussion above) fail to specifically state that  $\Delta\omega \cdot \tau_M \geq 1$ ; use various lanthanides (e.g., Pr, Nd, Sm, Tm, Er, Dy, and Ho), disclose that  $\Delta\omega$  is 6 ppm, and disclose that the contrast agent may be used in a MR system.

**Ward et al** disclose a new class of contrast agents for MRI based on proton chemical exchange dependent saturation transfer (CEST). In addition, Ward et al disclose that based on their experimental procedure, numerous candidate chemicals such as amino acids, sugars, nucleotides, and heterocyclic ring chemicals may be evaluated. Ward et al discloses that the chemical exchange rate should be as large as possible to enhance CEST effect, but it must remain in the slow to intermediate exchange rate domain to ensure that a spectral difference is maintained. The formula designated for the slow to intermediate exchange rate domain is  $\Delta\omega \cdot \tau \geq 1$  wherein  $\Delta\omega$  is the chemical shift difference and  $\tau$  is the single site proton lifetime(s). It should be noted that since  $\Delta\omega$  increases the magnetic field strength, the overall relationship between  $\Delta\omega$  and  $\tau$  is a function of the field strength of the MR experiment. Also, it should be noted that the exchange rate is often sensitive to proton concentrations,

temperature, and the ionic exchange (page 80, column 1, 'Chemical exchange rate'). A chemical shift between water and its proton exchange site on a candidate agent is advantageous. According to the equation,  $\Delta\omega \cdot \tau_M \geq 1$ , the larger the chemical shift between water and the agent, the greater the exchange rate may be without approaching the fast exchange limit. The larger  $\Delta\omega$  improves the specificity of the CEST effect. As a result, the magnetic field inhomogeneity for many tissues may exceed 2 ppm. Hence, a chemical shift beyond 2 ppm is desirable to avoid direct irradiation of water in the inhomogeneous regions. Also, a larger  $\Delta\omega$  permits the use of broadband irradiation to achieve saturation of the agent without direct effects on water protons which is advantageous because one avoids magnetic susceptibility resulting from poor agent saturation due to magnetic field variations. Another advantage of a large  $\Delta\omega$  is the reduction in the macromolecular water MT background because the further away the saturation pulse is applied from the water resonance, the less magnetization transfer between macromolecules and water protons will be observed for a given irradiation power due to reduced macromolecule saturation. Hence, the appropriate variables may be imputed into the formulae disclosed in Ward et al and various parameters determined (e.g., Ward et al disclose a formula for calculating the various parameters,  $\Delta\omega$ , Ms/Mo) [ pages 79-80]. The spectral difference of the CEST effects is determined by sweeping the irradiation frequency and monitoring the effects of the water resonance. The studies of Ward et al were conducted using a steady state irradiation over a range of frequencies  $\pm 8$  ppm from water (page 80-81, bridging paragraph).

Art Unit: 1616

**Dunand et al** disclose  $^{17}\text{O}$  NMR observation of coordinated water on  $[\text{Eu}(\text{DOTA})(\text{H}_2\text{O})]^{3+}$  isomers (see entire document, especially, abstract). In addition, Dunand et al disclose (1) that it is well known in the art that  $[\text{Ln}(\text{DOTA})(\text{H}_2\text{O})]^-$  complexes exist in two diastereoisomeric forms, m and M, which differ by the layout of their acetate arms (page 1506, column 2; page 1507, Scheme 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Aime et al using the teachings of Ward et al and Dunand et al and generate a contrast agent and uses thereof encompassed by Applicant's tetraazacyclododecane ligand formula as set for in independent claim 1 for the reasons set forth below. It would be obvious to a skilled practitioner in the art to generate (a) a contrast agent wherein  $\Delta\omega \cdot \tau_M \geq 1$  because Ward et al disclose a new class of contrast agents for MRI based on proton chemical exchange dependent saturation transfer (CEST) wherein the slow to intermediate chemical exchange rate is based on the above formula. Specifically, Ward et al discloses that while the exchange rate constant should be as large as possible to enhance the CEST effect, it must remain in the slow to intermediate exchange rate domain to ensure that a discrete spectral difference between water and the agent is maintained (page 80, 'Chemical exchange rate'). Hence, a skilled practitioner in the art would recognize the need to operate at conditions wherein  $\Delta\omega \cdot \tau_M \geq 1$ . Also, it should be noted that the contrast agents of Aime et al have  $\tau_M \geq 1$ , thus, it is obvious that  $\Delta\omega \cdot \tau_M \geq 1$ .



(b) It would be obvious to a skilled practitioner in the art to use various lanthanide metals because the replacement of one metal with another metal from the same chemical family would not drastically alter the overall properties of the contrast agent. In addition, it is noted that Dunand et al disclose that chelates containing DOTA-like ligands have two common arrangement and in the case of  $[\text{Ln}(\text{DOTA})-(\text{H}_2\text{O})]^-$  complexes, x-ray m-type structures are observed for La and C3 whereas M-type structures are observed for  $\text{Ln(III)} = \text{Eu, Gd, Dy, Ho, Lu, and Y}$ .

(c) It would be obvious to a skilled practitioner in the art to generate methods of using the contrast agent and a magnetic resonance system because both Dunand et al and Ward et al disclose the evaluation of CEST in various compounds. It should be noted that Ward et al, pages 80-81, bridging paragraph, disclose how CEST effects were determined by sweeping the irradiation frequency and monitoring the effects of the water resonance using steady state irradiation over a range of frequencies  $\pm 8$  ppm from water. Hence, it is obvious to generate a magnetization transfer signal when subjected to a radio frequency pulse.

(d) It would be obvious to a skilled practitioner in the art to use  $\Delta\omega$  greater than 2 ppm (e.g., 6 ppm) because Ward et al disclose that a chemical shift beyond 2 ppm is desirable to avoid direct irradiation of water in inhomogeneous regions. Also, a larger  $\Delta\omega$  permits the use of broadband irradiation to achieve saturation of the agent without direct effects on water protons. Another advantage of a large  $\Delta\omega$  is the reduction in the macromolecular water MT background.

Since all of the references are directed to DOTA-lanthanide complexes, the references may be considered to be within the same field of endeavor. Hence, the references are combinable.

## **SPECIFICATION**

10. The disclosure is objected to because of the following informality. A statement reading "This application claims benefit of provisional application 60/252,269, filed 11/20/2000." should be entered following the title of the invention or as the first sentence of the specification.

Appropriate correction is required.

## **ABSTRACT**

11. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (703) 308 - 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Art Unit: 1616

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

A handwritten signature in black ink, appearing to read 'D. L. Jones', is written over the typed name.

D. L. Jones  
Primary Examiner  
Art Unit 1616

November 3, 2003